Informalities

The following informalities have been corrected:

The reference to U.S. Patent No. 4,879,263 on page 11, line 11 has been deleted.

Applicant has updated the status copending applications 07/800,474 and 07/938,079 in the specification.

The Invention

The invention concerns the use of prostate antigens or their representatives in vaccines to produce an immune response to prevent or treat prostate cancer. While the prior art suggests the use of antigens uniquely associated with tumor tissue as components of antitumor vaccines, there is no suggestion to use antigens which are uniquely represented on host tissue for the tumor. Since the prostate is not an essential organ, elimination of the prostate gland, which may be a concomitant effect of the vaccines of the invention, does not adversely impact the general health of the subject. Thus, prostate cancer offers a unique opportunity for treatment with vaccines which characterize the host organ itself, rather than the malignant or metastatic nature of the cells *per se*.

Further, although it is recognized that prostate specific antigen (PSA) can be used in healthy experimental animals to generate antibodies for use in diagnosis, there is no suggestion that PSA or any other prostate antigen be used to elicit a protective or therapeutic immune response against prostate cancer.

Rejections for Lack of Utility Under 35 U.S.C. § 101 and § 112, First Paragraph

Claims 1-40 are rejected under 35 U.S.C. § 101 because the invention as disclosed is seen as inoperative and therefore lacking utility; the claims also were rejected under 35 U.S.C. § 112, first paragraph, for essentially the same reasons.

This appears more an issue of law than an issue of fact. Applicant acknowledges that no clinical data have been presented in the application. Applicant also acknowledges that various things might go wrong, as with any intended therapeutic or prophylactic method, e.g., as outlined by the Examiner on page 2-3 of the Office action. However, these are routine barriers to effective administration of any metabolically active compound and are routinely overcome by formulation and optimization of protocols. The fact that routine design of optimal patterns of administration is required does not undermine the fundamental utility of the invention.

The Office also asserts that "generation of an immune response against self, even if it is against tissue-specific antigens, could elaborate into an autoimmune response against other antigens of the host." This appears speculative at best. If the Examiner is aware of facts or references which establish that the possibility of such a reaction is sufficient to undermine the usefulness of the invention vaccines and methods, applicants respectfully request a declaration to that effect under 37 CFR 1.107(b).

The Office further asserts that so far no satisfactory vaccine has been approved for any form of cancer by the FDA. Applicants do not know whether this is or is not correct; however, it is not relevant to the

evaluation of the present invention. The test for utility is not approval for marketing by the FDA. This was clearly established in In re Anthony, 162 USPQ 594 (CCPA 1969) where the court said ". . . The FDA need not necessarily determine that a drug is commercially useful or useable before it may be 'useful' in the patent law sense." at page 604.

Further, the appropriate criterion is not that the utility of the claimed invention would be "believable" *prima facie*, but rather that the skilled artisan would not find it unbelievable on its face.

Given a facially credible assertion of utility, the burden is on the Patent Office to provide some evidence or reasoned argument from the evidence that the disclosed utility is in error. In re Gardner, 177 USPQ 396 (CCPA 1973), Ex parte Schundehutte, 184 USPQ 697 (BPAI 1974). See also, In re Gazave, 154 USPQ 92 (CCPA 1967), cited in MPEP § 608.01(p).

In this case the Office has provided no evidence to suggest that one of ordinary skill would find the stated utility "to be of such a 'speculative', abstruse or esoteric nature that it must inherently be considered unbelievable, 'incredible' or 'factually misleading'.". (In re Gazave (*supra*).) Accordingly, the Office has not met its burden of providing sufficient facts or reasoning to show that the statements made in applicants' specification, which are not inherently incredible, are not to be believed.

Rejections Under § 112, First Paragraph Related to Scope

The specification is objected to under 35 U.S.C. § 112, first paragraph, and claims 1-40 are rejected, as overbroad.

First, the office asserts that the specification fails to disclose overrepresented prostate antigens other

than PSA, PSMA and PAP. The Office states that the specification has not provided sufficient direction or guidance to one of skill in the art to properly select prostate antigens other than PSA, PSMA and PAP, which are required to enable the broadly claimed compositions and methods. On this basis the Office concludes that undue experimentation would be required of one skilled in the art to practice the broadly claimed compositions and methods using the teaching of the specification alone.

However, the specification expressly teaches that antigens suitable for the practice of the invention include any antigen which is overrepresented on prostate tissue. The specification expressly defines what is meant by "overrepresented," on page 5, lines 15-24.

> the concentration of this antigen in prostate is sufficiently higher than its concentration in any other tissue such that the prostate can effectively be targeted by the immune response raised against this antigen with relative sparing of other organs or tissues. Sparing can be measured by overall clinical toxicity to the subject. Toxicity to the subject is generally grade 3 or less, preferably grade 2 or less most preferably grade 1 or grade 0.

Applicants believe that this express and definite guidance as to selection of antigens, which is based on conventional assessments of therapeutic toxicity, provides sufficient guidance to one of ordinary skill in the art to determine by routine methods which antigens are suitable for use in the present invention. The Office appears not to have considered this express guidance in the specification.

It should be noted that the Office has the burden of establishing a lack of enablement. In re Hogan, 194 USPQ 527, 539 (CCPA 1977). In this case, no evidence has been adduced to demonstrate that one skilled in the art would find the specification nonenabling in light of its discussion and exemplification. Additionally, applicants have not been provided with an assessment of enablement under the "standard of reasonableness" to which they are entitled, given the nature of the invention and the state of the art:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed...

In re Jackson, 217 USPQ 804, 807 (Bd. App. 1982, cited with approval in Wands, 8 USPQ2d at 1404).

Even when "unpredictability" may create reasonable doubt as to the accuracy of a broad statement supporting enablement, and even when the statement is, on its face, contrary to generally accepted scientific principles, the CCPA, has clearly articulated that

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts

> the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with a contested statement.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1967).

The Office has not explained why it doubts the truth or accuracy of the statement regarding selection of antigens and has not backed up its own assertions of undue experimentation with acceptable evidence or reasoning which is inconsistent with the statement on antigen selection.

It should be remembered that applicants do not claim to have invented any prostate antigens or immunologically active portions of such antigens. The present invention lies in the recognition that antigens which are overrepresented in the prostate, as expressly and clearly defined in the specification, can be beneficially used as vaccines to induce an antitumor immune response in a potential or actual prostate tumor-bearing subject. Therefore, applicants are not required to teach how to make immunologically active portions of each and every possible such antigen but can, instead, rely on conventional methods in the art, such as known methods of identifying peptides which mimic epitopes of protein antigens.

The fact that the claims may encompass many different antigens and immunologically active portions does not require the practitioner to make and test every possible one of them. The function of the claims is to provide a description which one of ordinary skill can use to determine whether any composition or method is included within the scope of protection of the patent. The specification, as required, provides adequate guidance, as discussed above, to

routinely determine whether any given antigen or immunologically active portion is suitable for the practice of the claimed invention, as required for enablement under § 112. Applicants are not aware of any legal requirement that all potential prostate-specific antigens must be taught when the invention lies in knowing what to do with the antigens once they are found.

Rejections Under § 112, First and Second Paragraphs

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter, as to the reference in claim 6 to a "neoadjuvant". The term "neoadjuvant" has been deleted from claim 6. Accordingly, this rejection may be withdrawn.

Claims 1-40 are rejected under 35 U.S.C. § 112, first and second paragraphs, based on the following recitations: "at least one antigen overrepresented in the prostate gland", "peptide", "a fragment thereof", "portion ", "portion thereof", "active ingredient", "effective portion", "portion being less than the complete antigen" and "exhibits posttranslational modification different from those of PSA produced in human cells."

The Office considers these terms indefinite simply "because their characteristics are not known." This does not provide much guidance to applicants as to the basis for rejection.

As to the meaning of the first phrase listed, applicants note that the specification expressly defines this in terms of toxicity parameters, as cited above. See specification, page 5, lines 15-24. It is believed that this definition, which is based on conventional clinical assessments of therapeutic toxicity, would be clear to one

of ordinary skill in the art, absent any evidence to the contrary. The Office has not provided any evidence that this express definition would not be clear to the practitioner or not enabled.

Applicants do not understand the objection to the term "peptide," which is recited only in claims 2 and 3. This simply represents a subset of the antigens that can be used as explained on page 6, lines 4-13. This appears to be a scope rejection since the Office further states

> This language is vague and indefinite since it encompasses potentially thousands of different proteins or peptides and it is not apparent from the disclosure which particular proteins or peptides are being referred to.

Applicants incorporate their response to this rejection as set forth above.

Regarding the phrase "active ingredient," applicants have amended the claims to point out more clearly the function for which the recited ingredient is "active." Thus, claim 1 now recites "a composition comprising an ingredient which is active to induce said immune response" where the referenced immune response is the "antitumor immune response" recited in the preamble. Each of the other claims which recites "active ingredient" also have been similarly amended. Any indefiniteness is obviated by the present amendments.

The specification expressly defines an "immunologically effective portion" to mean "that portion of an antigen, taken alone, which is capable of eliciting an immune response". See page 5, line 28-page 6, line 3. The specification also notes that, typically, such portions

represent an individual epitope or a specific subset of the epitopes that comprise the complete antigen. This term is generally understood in the art.

The Office also considers indefinite the phrases "a fragment thereof", "portion ", and "portion thereof." Applicants have amended the claims to recite consistently "an immunologically effective portion" which is expressly and clearly defined in the specification as cited above. Claims 1, 3, 9, 15 and 22 have been amended to state the "fragment" of the antigen or mimicking antiidiotypic antibody is an "immunologically effective portion". Other claims which recited only a "portion" or "effective portion" of an antigen have been amended to recite more fully that the portion is an "immunologically effective portion," either by expressly inserting this full description into the claim (e.g., claims 16 and 36), or by amending a dependent claim to reference more clearly the full description in an independent claim (i.e., by reciting "said portion" instead of "portion" as in dependent claims 14 and 22, for instance).

As to the phrase "said portion being less than the complete antigen," which is recited only in claim 28, this phrase is intended to distinguish prior art full-length antigen-containing compositions.

The expression "exhibits posttranslational modifications different from those of PSA produced in human cells," which is recited only in claim 25, is expressly defined on page 11, lines 17-29:

> The preparation of recombinant forms of protein antigens in a variety of host cells results in a variety of posttranslational modifications which affect the immunogenicity and other pharmaceutical properties, such as

> pharmacokinetics, of the product. Accordingly, although human prostate-specific antigen (PSA) isolated from human tissues has been used to induce the production of antibodies for diagnostic use, the immunogen prepared in this way differs from the immunogen as prepared in nonhuman cells, such as insect cells. The posttranslational modifications peculiar to the recombinant host result in alternations in glycosylation pattern, folding, and the like.

Thus, the recited posttranslational modifications of the recombinantly produced antigen, which differ from those of PSA produced in human cells, represent alterations in glycosylation pattern, folding, and the like, and distinguish from the native protein.

Rejections Under § 112, Second Paragraph

Claims 1-40 also are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

A) Claims 1-40 are considered indefinite in the recitation of "vaccine" and "composition". The Office suggests that the pharmaceutically acceptable carrier and the effective amount of the active ingredient be recited in the claims.

This has been done. Claims 8, 15, 21, 22, 28 and 34 recite a vaccine or composition "formulated for parenteral administration." Support for this amendment may be found in the specification, for instance at page 15, lines 25-29. Ordinarily skilled persons would understand that for parenteral administration, antigens are conventionally formulated in a solution with some sort of pharmaceutically acceptable carrier, as taught in

Remington's Pharmaceutical Sciences cited in the specification. The claims already recite the function of the composition as eliciting an antitumor immune response to prostate tumors, in the preamble.

B) Claims 3 and 9 are considered indefinite in the recitation of "PSA", "PSMA" and "PAP" because these terms should be spelled out; claims 3, 9 and 16 have been thus amended.

C) Claim 6 is considered indefinite in the recitation of "neoadjuvant." Claim 6 has been amended accordingly.

D) Claim 34 is considered indefinite in the recitation of "with the proviso that said antigen is other than human prostate specific antigen (PSA) produced in human cells" because the Office is unclear whether this refers to antigens other than PSA or to antigen derived from cells other than its natural host.

Applicants have amended claim 34 to point out more clearly that the proviso excludes only human PSA which is produced in human cells; thus, PSA produced in non-human cells or other antigens produced in human or other cells is not excluded. This distinguishes native PSA.

Rejection Under § 103

Claims 1-40 are rejected under 35 U.S.C. § 103 as being unpatentable over Chu *et al.* (U.S. Patent No. 4,446,122) in view of Dai *et al.* (FASEB J., 1988), Deguchi *et al.* (Cancer Research, 1986), Brown *et al.* (U.S. Patent No. 5,262,177) and Alving (J Immunol Methods, 1991) and the art-known vaccine and recombinant technology acknowledged throughout the specification.

Chu *et al.* is said to teach the characterization of the PSA antigen, particularly its use in immune-specific chemotherapy (column 6, paragraph 1) and its use in preparing diagnostic antibodies and in vaccine preparation (at column 7, paragraph 3). Dai *et al.* is said to teach the generation and characterization of antiidiotypic antibodies for prostate tumors (see Abstract). Deguchi *et al.* is said to teach the use of PAP-specific antibody conjugates for the treatment of prostate tumor. In view of the above characterizations of the cited documents, the Office asserts that "the prior art recognized the use of prostate- specific antigens in the derivation of therapeutic regimens to treat prostate cancer." Therefore, the Office concludes that one of ordinary skill would have been motivated to select and evaluate the efficacy of prostate-specific antigens as vaccines in the treatment of human prostate cancer. The Office also concludes that, from the teachings of the references, one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention.

The references cited by the Office do not suggest the use of antigens which are uniquely represented on host tissue in antitumor vaccines, as required by the present invention. The cited portions of Chu do not suggest this. Teaching that an antigen may be targeted for immune-specific chemotherapy by injecting monoclonal antibodies conjugated to a toxin (column 6, paragraph 1) does not suggest that the same antigen may be used in a vaccine actively to induce a host immune response to the tumor. Further, Chu *et al.* clearly use the term "vaccine" (column 7, paragraph 3) only in the context of raising diagnostic antibodies to PSA in animals: "For the preparation of immunogens suitable for

preparing diagnostic antibodies against the human prostate antigen, conventional vaccine preparation techniques can be used." The paragraph goes on to discuss use of the "vaccine" in rabbits, goats and other mammals which evidently are not tumor-bearing subjects or at risk for same.

The abstract by Dai *et al.* is said to teach the generation and characterization of antiidiotypic antibodies for prostate tumors, but not their use to elicit immune responses to combat prostate tumors. The abstract describes the characterization of antiidiotypic antibodies for a particular rat prostate tumor. As to use of these antibodies, the authors at best speculate that "[t]his anti-idiotypic antibody is of potential value for modulating the immune response of Dunning rat prostate tumor." It is unclear from the abstract exactly what type of modulation is intended, whether stimulation or suppression, since either would be plausible given the context of the experimental animal model. Further, Dai does not suggest an immunogen derived from the host tissue, as required by the claims.

Deguchi *et al.* is said to teach the use of PAP-specific antibody conjugates for the treatment of prostate tumor. Passively administering an antibody conjugated to a toxin does not suggest the use of the target antigen in a vaccine actively to induce a host immune response to the tumor. Even if somehow immunochemotherapy generally is seen to suggest antitumor vaccines, one of ordinary skill would not extrapolate such a suggestion in this particular case, based on an experimental rodent model with an implanted human tumor.

As noted by the Office, the remaining references merely provide enabling technologies for various known

elements of some of the claims, such as expression systems. Therefore, these references cannot provide the suggestion, missing in the first three references, to make the invention as claimed. Nor do the other references provide any reasonable expectation of success. Accordingly, there is no *prima facie* obviousness and the rejection of claims 1-40 under § 103 may properly be withdrawn.

Conclusion

In view of the foregoing, it is believed that claims 1-40 are in condition for allowance, and passage of these claims to issue is respectfully requested.

Respectfully submitted,

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